

Treatment of Idiosyncratic Drug-Induced Liver Injury Using Steroids

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ABSTRACT

Idiosyncratic drug-induced liver injury (DILI), when severe, can be associated with significant morbidity and mortality. Currently, there are no specific therapies for DILI, apart from corticosteroids for drug-induced autoimmune hepatitis caused by drugs such as nitrofurantoin or minocycline. We present 2 cases of DILI that improved with corticosteroid therapy despite the lack of autoimmune features by serology or histology. The current observations make a strong case for formally testing corticosteroids in a controlled trial in patients with suspected DILI.

INTRODUCTION

Corticosteroid use is common in patients with idiosyncratic drug-induced liver injury (DILI).¹ Although the mainstay of idiosyncratic DILI therapy is the withdrawal of the offending agent, the use of ursodiol and steroids may be justified in instances where DILI cannot be distinguished from autoimmune hepatitis or when it presents with an autoimmune phenotype because of medications such as nitrofurantoin or minocycline. We present 2 well-characterized cases of DILI without autoimmune features and yet responding rapidly to corticosteroids, making a case for further investigating their use as a treatment option.

CASE REPORT

Patient 1: A 61-year-old woman with small bowel gastrointestinal stromal tumor was started on imatinib 400 mg a day. Approximately 3 months after initiation of imatinib, she had a marked increase in the liver enzymes to alanine transferase (ALT) 758 U/L, aspartate transferase 354 U/L, and total bilirubin of 0.8 mg/dL, with normal alkaline phosphatase. The patient also became symptomatic with abdominal distention and pedal edema. Imatinib was discontinued. Thorough workup excluded competing etiologies with negative viral hepatitis B and C antibodies and autoimmune hepatitis panel, including antismooth muscle antibody and anti-LKM1. A liver biopsy showed widespread perivenulitis with extensive zone 3 necrosis including bridging necrosis. A mild to moderate portal inflammatory infiltrate of lymphocytes was present with intermingled eosinophils and neutrophils. Interface hepatitis was only mild and not indicative of autoimmune hepatitis. Bile ducts were present in all portal tracts with only mild epithelial damage (Figure 1).

After a brief downward trend, the liver enzymes increased to a peak ALT of 1184 U/L, aspartate transferase of 693 U/L, and total bilirubin of 1.7 mg/dL. The patient was empirically initiated on oral budesonide (9 mg/d) with a slow taper. This treatment resulted in an immediate decline in enzymes and symptomatic improvement. Because of zone 3 necrosis and suspected dose-related toxicity, we tested for drug-metabolizing enzyme polymorphisms and found her to be a cytochrome P450 3A5 poor metabolizer. After 3 months of treatment and complete normalization of liver enzymes, she was rechallenged with imatinib at 200 mg every other day with careful monitoring while she remained on 3 mg of budesonide. However, her liver enzymes rapidly increased, prompting permanent discontinuation of imatinib (Figure 1). The dosage of budesonide was increased to 9 mg/d, with rapid improvement in her liver enzymes. At her most recent visit, her liver enzymes were normal and her budesonide was completely discontinued after the prolonged taper.

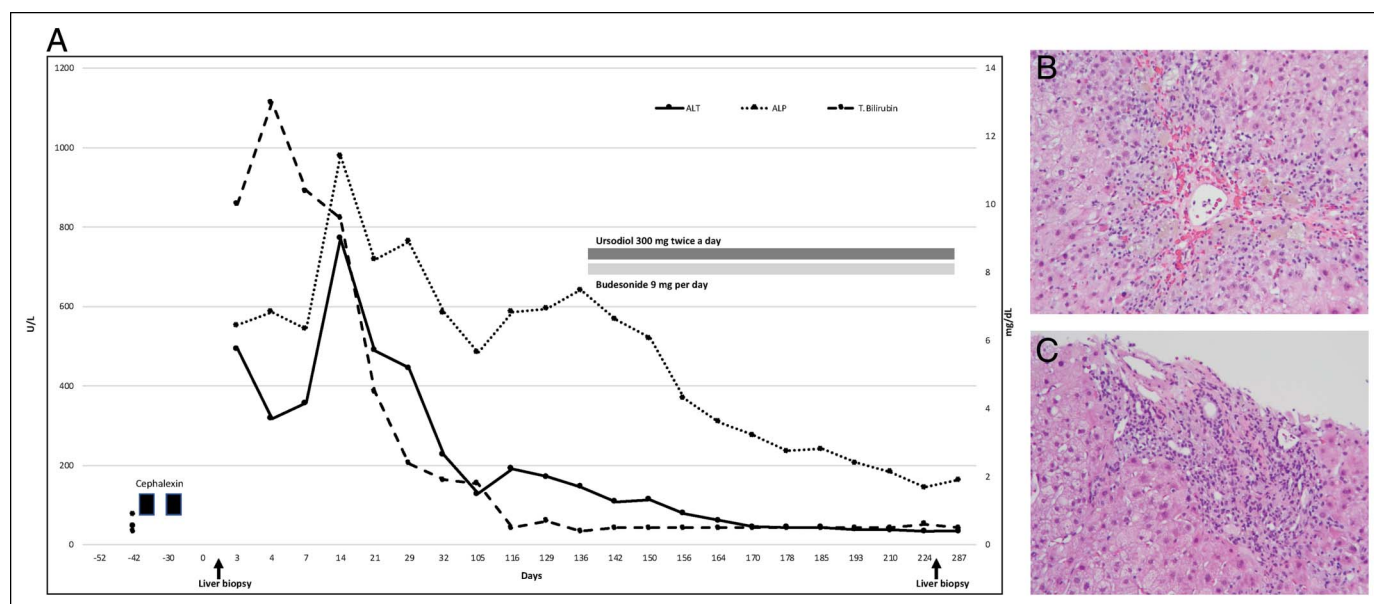


Figure 1. (A) Liver test trends in relation to exposure to the implicated drug (imatinib) and initiation of steroid. The rechallenge with imatinib was associated with a repeat increase in alanine aminotransferase and total bilirubin levels. (B) Perivenulitis with necrosis and an inflammatory infiltrate of lymphocytes and pigmented macrophages (hematoxylin and eosin [H&E] 10×). (C) Moderate portal inflammation consisting mainly of lymphocytes with a few intermingled eosinophils. Mild interface hepatitis, not indicative of autoimmune hepatitis, is present. Bile ducts are present and show minimal epithelial damage (H&E 100×). ALT, alanine transferase; ALP, alkaline phosphatase.

Patient 2: A 61-year-old woman with breast cancer was prescribed a 10-day course of cephalixin (500 mg twice daily orally) after tumor resection. Two weeks later, she had a repeat course of cephalixin at a similar dosage and duration for cellulitis after port placement for chemotherapy. Approximately 1 month later, she developed nonspecific symptoms including fatigue and syncope. Blood work revealed cholestatic pattern

elevation in liver enzymes with a total bilirubin of 10.4 mg/dL, ALT of 129 U/L, and alkaline phosphatase of 587 U/L with a corresponding R-factor of 0.7. Serologic workup excluded acute viral and autoimmune hepatitis. Liver ultrasound revealed no biliary dilation. A liver biopsy showed cholestatic hepatitis with mild portal inflammatory infiltrate of lymphocytes and eosinophils. There was no interface

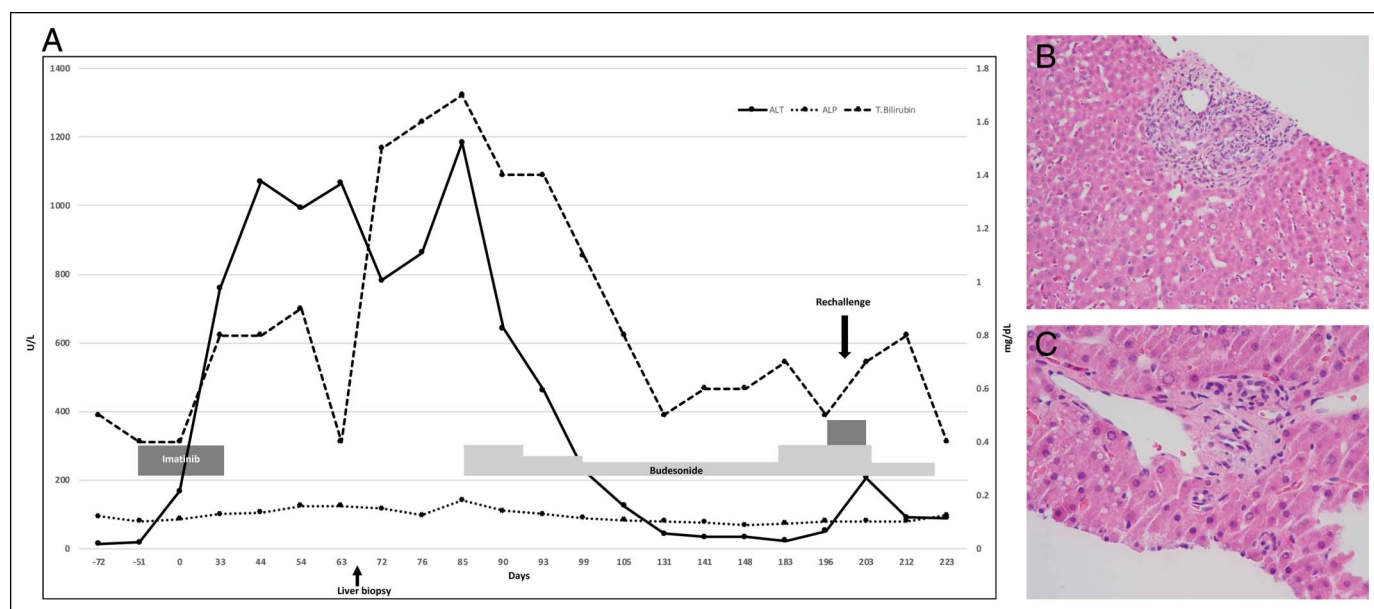


Figure 2. (A) Liver test trends in relation to exposure to cephalixin and initiation of budesonide 142 days after the onset of liver injury. The timing of the liver biopsy indicated on the x axis. (B) Portal tract with mild inflammatory infiltrate of lymphocytes and eosinophils with marked biliary epithelial damage. There is no interface hepatitis (hematoxylin and eosin [H&E] 10×). (C) Portal tract with no inflammation. Bile ducts are present (H&E 100×). ALT, alanine transferase; ALP, alkaline phosphatase.

hepatitis. Foci of inflammation and clusters of foamy macrophages were scattered throughout the lobules. Bile ducts were present in all portal tracts, but there was marked bile duct damage with flattening of the epithelium and nuclear overlapping and loss. Bile plugs were present within the canaliculi. Although the total bilirubin improved, her liver enzymes remained elevated, prompting a referral to our institution. The follow-up biopsy showed minimal ductular proliferation without inflammation, bile duct damage, or bile duct loss (Figure 2).

Despite convincing evidence for DILI based on temporal association, liver histology, and adequate exclusion of competing etiology, persistent liver test abnormalities after attempted rechallenge prompted us to start budesonide at 9 mg per day and ursodiol at 600 mg per day 142 days after DILI onset. The patient responded with dramatic symptom improvement and liver test normalization in a 2 weeks' span. Continued treatment with prolonged steroid taper after 3 months at maintained initial dose resulted in further improvement.

DISCUSSION

For both suspected DILI cases presented here, we excluded competing etiologies, including autoimmune hepatitis. In both instances, the patients were under the care of oncologists who could not initiate (patient 1) or resume (patient 2) chemotherapy until normalization of the liver test was achieved. Because these tests remained persistently elevated, the clinicians reported to a trial of empiric budesonide, which resulted in a dramatic improvement in liver tests. Corticosteroid treatment of DILI is not a standard of treatment but has been well documented. In a review of patients who received this treatment in the DILI Network prospective study, patients were younger, largely women, and with more severe serological derangements. It was also noted that this group demonstrated a higher

mortality rate, possibly attributable to the fact that these patients suffered from worse liver injury before treatment.¹ Relatively widespread empiric use of corticosteroids in DILI and our current observations make a strong case for more formal investigations into its efficacy as a treatment in patients with suspected DILI.

DISCLOSURES

Author contributions: S. Sundaram, R. Vuppalanchi, and R. Saxena wrote the manuscript. N. Chalasani wrote and revised the manuscript, and is the article guarantor.

Financial disclosure: N. Chalasani, R. Vuppalanchi, and R. Saxena have consulting agreements with pharmaceutical companies, but they declare that those activities are not directly or significantly related to this study. Both the patients were enrolled in the Drug-Induced Liver Injury Network (DILIN) Prospective Study, but this study is not submitted on behalf of the DILIN.

Informed consent was obtained for this case report.

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